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| EXAMINER | |
|---|---|
| HADDAD, MAHER M | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1644 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/563,389 | WELSH ET AL. | |
| | Examiner | Art Unit | |
| | Maher M. Haddad | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *20 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *45-75* is/are pending in the application.

4a) Of the above claim(s) *51-61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45-50 and 62-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/25/07 and 3/12/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 45-75 are pending.

2. Applicant's election with traverse of Group I, claims 45-75, drawn to a substantially pure consecutive and anti-angiogenic polypeptide, comprising the central region of human histidine rich glycoprotein (HRGP) corresponding to SEQ.ID.NO:2, subfragments thereof and a pharmaceutical composition thereof and the species of SEQ ID NO: 1, filed on November 20, 2008, is acknowledged.

Applicant's traversal is on the grounds that there would be no undue burden for the Examiner to search the full scope of the subject matter of claims 45-83. Moreover, Applicant notes that Hulett et al. do not disclose "a substantially pure consecutive.., polypeptide" as recited in the currently pending claims. Hulett et al. have not isolated any polypeptides form the histidine rich glycoprotein (HRGP), but only the whole protein from mouse and rat. Thus, there is no disclosure in Hulett et al. of isolated polypeptides derived from the HRGP that also provide an anti-angiogenic effect, as recited in the currently pending claims. With respect to the species Applicant traverses on the grounds that there would be no undue burden to search each of the claimed species. This is not found persuasive because Applicant's traversal is moot by the cancelation the non-elected invention of claims 76-83. With respect to the species these species are distinct species because their structures and modes of action are different which, in turn, address different therapeutic endpoints.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 51-61 (non elected species) are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions.

4. Claims 45-50 and 62-75 are under examination as they read on a substantially pure consecutive and anti-angiogenic polypeptide, comprising the central region of human histidine rich glycoprotein (HRGP) corresponding to SEQ.ID.NO:2, subfragments thereof and a pharmaceutical composition thereof and the species of SEQ ID NO: 1.

5. The specification is objected to under 37 CFR 1.821(d) for failing to provide a sequence identifier for each individual sequence. Page 2, line 14 has described a HRGP sequence that must have a sequence identifier. Correction is required.

6. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

7. The Oath/Declaration is objected to because Sweden 0301988-2, listed on first line of the specification is not listed in the Oath.

8. Applicant's IDS, filed 1/25/07 and 3/12/08, is acknowledged.

9. The term "corresponding to" in claims 45, 46 and 48 is objected to because it is not clear whether "corresponding to" is open or close language, and what species is being claimed that "corresponding to" the claimed sequence. It is suggested that the claim be change to recite "as shown in", "as set forth in" or "of".

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

*The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.*

11. Claims 45-50 and 62-75 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a substantially pure consecutive and anti-angiogenic polypeptide consisting of SEQ ID NO: 2 or SEQ ID NO: 1, and a composition thereof, does not reasonably provide enablement for the polypeptides claimed in claims 45-50 and 62-75. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The specification on page 2, lines 35-37 discloses that HRGP was suggested also, under certain circumstances, to promote angiogenesis and to attenuate the anti-angiogenic effect of TSP-1 by complex-formation between the two proteins. Further, the specification on page 9, lines 40-41 discloses that presently the separate domains are shown to be responsible for different biological activities, one being anti-angiogenic, another being pro-angiogenic. The specification on page 10, lines 24-35 discloses that the central region of HRGP (His/Pro region) (listed as SEQ ID NO: 2) is demonstrated to be the region responsible for the anti-angiogenic properties of HRGP. The isolated central region (His/Pro-rich domain) of human HRGP inhibited chemotaxis as potently as the mature protein. Surprisingly, the truncated version His 4 did not inhibit endothelial cell chemotaxis, even though it covers the complete central region. The reason for this is most probably that an improper folding of the protein prevents the active site of the central region from being correctly presented. The specification on page 10, lines 36-41 discloses that a 25 amino acid long subfragment of the central region $(GHHPH)_5$, located in direct succession to Pep2, and corresponding to amino acids 365-389 of mature human HRGP was clearly

demonstrated not t be active for inhibiting angiogenesis, as shown in experiment 9. This further strengthens the hypothesis of a minimal functional entity of HRGP, not corresponding to the whole part of the central region, but rather to a short fragment such as Pep2, or any subfragments thereof. Moreover, the specification on page 12, lines 36-39 discloses that PEP8 peptide (SEQ ID NO: 15) which is derived from the central region of human HRGP was proven not to be effective in a chemotaxis assay (see table 2).

The claims are directed to any polypeptide comprising the central region of human histidine rich glycoprotein (HRGP) corresponding to SEQ ID NO: 2, however the specification discloses on page 10, lines 32-35 that the truncated version His 4 did not inhibit endothelial cell chemotaxis , even though it covers the complete central region (claimed SEQ ID NO:2). The specification discloses that the reason for this is most probably that an improper folding of the protein prevents the active site of the central region from being correctly presented. Similarly, a polypeptide comprising SEQ ID NO: 2 would be expected to be non-functional due to the improper folding. It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions can result in substantially different biological activities. Applicant has not enabled structurally related and unrelated compounds comprising "central region of HRGP" which would be expected to have difference in their activities.

Claims 46 and 48 recite "corresponding to", corresponding to is considered open language and would read also on a larger polypeptide.

Claim 47-50, reads on any subfragment derived from SEQ ID NO: 2, however, the specification discloses that a 25 amino acid long subfragment of the central region, located in direct succession of Pep2 (claimed SEQ ID NO:1) was clearly demonstrated not to be active for inhibiting agniogenesis (see page 10, lines 36-40). The specification on page 12, lines 36-39, discloses that Pep8, which is derived from Pep2 was proven not to be effective in a chemotaxix assay. Applicant has not identify a motif that is responsible for the anti-anti-angiogenic activity of the central region of HRGP, as evidence by Pep 11 which a non-consecutive amino acid derived from the central region of human HRGP, but fails to inhibit chemotaxis. Yet, Applicant claims any subfragment of the central region of human HRGP having amino acid length of between 3-35, 3-25, 3-20, 3-15, 3-10, or 3-8 amino acids. The skilled in the art would not know which 3-35 amino acids are responsible for the anti-angiogenic activity of the claimed central region of human histdine rich glycoprotein.

Claims 66-74 recite a pharmaceutical composition of the claimed subfragments, however, the specification fails to demonstrate an *in vivo* activity for the claimed subfragments. Inhibiting chemotaxis alone is insufficient to provide in vivo efficacy of the claimed subfragments. In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the method of inhibiting angiogenesis indices adhesion inhibitory peptide such as adhesion-based molecules can be species – and model-dependent, it is not clear that reliance on the polypeptide of SEQ ID NO: 2 or His5 that inhibits angiogenesis accurately reflects the relative efficacy of the claimed "anti-angiogenic" in a subject.

Finally, claim 75 is at issue. Claim 75 recites an effective amount of Zn2+. However, SEQ ID NO: 1 (Pep2) and the claimed subfragments all are missing the metal-binding domain $(GHHPH)_5$ of the HRGP. It is not clear how the claimed Zn2+ would act as a cofactor for HRGP.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view on the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

*(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.*

*(e2) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.*

*The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).*

13. Claims 45, 47, 49-50, 62-66 are rejected under 35 U.S.C. 102(b) as being anticipated by Koide et al Biochemistry 25:2220, 1986), IDS reference.

Koide et al teach the following subfragment of the central region of human HRGP (claimed SEQ ID NO: 2):

a) the consensus sequence GHHPH (Gly-His-His-Pro-His) which correspond to region 106-110 of claimed SEQ ID NO: 2 (see abstract, Figure 4 A),
b) FHWGGHERSSTTKPPFKPHGS (245-265 of HRGP),
c) RDHHHPHKPHEHGPPPPPDE (266-285 of HRGP),
d) RDHSHGPPLPQGPPPLLPMSC (286-306 of HRGP)
e) DLHPHKHHSHEQHPHGHHPH ((330-349 of HRGP),
f) AHHPHEHDTHRQHPHGHHPH (350-369 of HRGP) and
g) GHHPHGHHPEGEHPHGHHPH (370-389 of HRGP) (see Fig. 3 under Types III-V internal repeats).
h) HKHHSHEQHPHGHHPHAHHPHEHDTHRQHP (334-363 of HRGP, see Fig. 5, under HRG (334-363)).
i) PHKPHEHGPPPPPDERDHSHGPPLPQGPPPLLP (271-303 of HRGP, see Fig. 6, under HRG (271-303)).

Claim 45 is included because Koide et al teach the human HRG polypeptide comprising the central region of HRGP (see Fig. 2 in particular). There term "comprising" in claim 45 is open-ended. It would open up the claimed SEQ ID NO: 2 include the full length of the human HRG.

While the prior art may by silence with respect that the referenced polypeptides are the anti-angiogenic, the prior art reference teaches that same polypeptide/subfragments of the central region of human HRGP. Accordingly, being "anti-angiogenic" is inherent.

It is noted the claims 63-65 are constructed as product by process. However, the patentability of a product does not depend on its method of production. In re Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985), MPEP 2113. It is Applicant burden to show that the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product.

The reference teachings anticipate the claimed invention.

14. Claims 45-51 and 62-74 are rejected under 35 U.S.C. 102(b)/(e) as being anticipated by WO 02/076486/US. 20050042201 as is evidenced by the specification on page 3, lines 5-10 and lines 24-25.

The teachings of US `201 corresponds to WO `486.

The `201 publication teaches and claims a composition comprising a substantially pure histine-rich glycoprotein polypeptide (see published claims 1, 16 and 54) and further comprising an anti-angiogenic agent (see published claim 2) such as angiostatin and a COX-2 inhibitor (anti-inflammatory agent) (see published claim 3), a pharmaceutical carrier (see published claim 4), wherein said polypeptide is an HRGP fragment (see published claim 5), wherein said fragment comprises the central domain of intact HRGP (claimed SEQ ID NO:2) (see published claims 7 and 16), wherein said fragment comprises at least one tandem repeat of the pentapeptide [H/P]-[H/P]PHG (see published claim 9). The composition further comprising an anti-neoplastic agent such as taxol (see published claims 10 and 12. Fig. 3 of the `201 publication teaches the his/pro region as 330-439 of the HRGP.

Further, the referenced central domain of intact HRGP is claimed SEQ ID NO: 2, as is evidenced by the specification on page 3, lines 5-10 that in WO 02/076486, the inventors for the first time describe the use of HRGP polypeptides, or its central regions, for the inhibition of anglogenesis. Moreover, the specification on page 3, lines 24-25 discloses that the central region of human HRGP, defined as amino acid region 240-390 (as seen in SEQ ID NO:2) of mature human HRGP.

Claim 48 is included because the term "corresponding to region 330-364 of mature human HRGP" is open-ended. It would open up the subfragment to read on the central domain of intact HRGP (claimed SEQ ID NO: 2). Given that the central domain of intact HRGP is a subfragment itself.

It is noted the claims 63-65 are constructed as product by process. However, the patentability of a product does not depend on its method of production. In re Thorpe, 227 USPQ 964, 966 (Fed. Cir. 1985), MPEP 2113. It is Applicant burden to show that the manufacturing process steps would be expected to impart distinctive structural characteristics to the final product.

The reference teachings anticipate the claimed invention.

15. Claims 47, 49, 50 and 62-65 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 02/064621, IDS reference.

The ` 621 publication teaches a pentapeptide from the H/P domain having the sequence (His,pro)-(His,Pro)-Pro-His-Gly (published SEQ ID NO: 7), wherein the pentapeptide is His-His-Pro-His-Gly (published SEQ ID NO: 8), His-Pro-Pro-Gly (published SEQ ID NO: 9) or (Pro-Pro-Pro-His-Gly (SEQ ID NO:10) to inhibit angiogenesis (see published claims in particular).

Claims 62-65 are included because a polypeptide is a polypeptide irrespective how it is made.

The reference teachings anticipate that claimed invention.

16. Claims 47, 49, 50, 62-68 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat. No. 7,294,515.

The `515 patent teaches a 25 amino acid subfragment $(GHHPH)_5$ of the central region of human HRGP (see patented SEQ ID NO: 3).

```
Qy          126 GHHPHGHHPHGHHPHGHHPHGHHPH 150
                ||||||||||||||||||||||||||
Db            1 GHHPHGHHPHGHHPHGHHPHGHHPH 25
```

The patent teaches this peptide $(GHHPH)_5G$ defines the metal-binding domain within the intact sequence of the 80-kDa protein known as HRG. The `515 patent teaches that the peptide to be sequence is added to the beads in sodium phosphate buffer (composition) at pH 8.0 and incubated for 24 hrs at 4°C with gentle shaking (see col., 37, lines 64-66). The reference teaches that same subfragment as claimed, thus the functional activity of the subfragment is considered inherent.

Claims 62-65 are included because a polypeptide is a polypeptide irrespective how it is made.

The reference teachings anticipate the claimed invention.

17. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B. O'Hara can be reached on (571) 272-0878. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

February 2, 2009

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